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Projuvenoids: Synthesis and Biological Evaluation of Sulfenylated, Sulfinylated, and Sulfonylated Carbamates

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Applying the proinsecticide principle developed earlier for neurotoxic carbamate insecticides, a series of new *N*-sulfenylated, *N*-sulfinylated, and *N*-sulfonylated derivatives of fenoxycarb were synthesized and evaluated for juvenile hormone mimicking activity. Laboratory evaluations of the compounds using *Pieris brassicae* and *Sitophilus oryzae*, as well as field experiments using *Bemisia tabaci*, showed that several symmetrical *bis*carbamates with either a sulfenyl or sulfinyl bridge possessed higher activity than the parent carbamate. From the unsymmetrical compounds containing biologically inert derivatizing moieties, one of the sulfenylated *bis*carbamates also showed improved activity against *P. brassicae*. The changes in the biological activity of the sulfur-containing derivatives compared to that of the parent compound are attributed to the modified physicochemical characteristics, i.e., increased lipophilicity facilitating penetration, transport, as well as protection of the compound from metabolism.

Key words: juvenile hormone analogs, fenoxycarb, proinsecticides, sulfenylcarbamates, sulfinylcarbamates

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INTRODUCTION

The elucidation of the structures of juvenile hormones (JH*) has provided novel lead compounds for the research and development of safe insect control agents (Henrick, 1982, 1991). While analogue-synthesis has largely been based on structural similarity to the natural sesquiterpene hormone, several new compound types that induce characteristic JH-like symptoms have also been discovered and commercialized (for an overview, see Ujváry et al., 1992).

During their extensive studies with JH analogs, Sláma and Romanuk (Sláma and Romanuk, 1976; Sláma, 1981; Wimmer et al., 1988) developed the so-called juvenogens which are cleavable derivatives of terpene alcohols that upon hydrolysis within the insect body release the biologically active juvenoid. For carbamate insecticides with high acute mammalian toxicity, an alternative derivatization technique was developed by Fukuto and co-workers (Fahmy et al., 1974; Fahmy and Fukuto, 1983; Fukuto, 1983). These so-called proinsecticides are (bio)activated into the active toxicant in the target organism and, importantly, possess substantially reduced mammalian toxicity, but remain similarly toxic to the target species as their parent carbamates (reviewed by Drabek and Neumann, 1985; Prestwich, 1990; Umetsu, 1992).

In our search for new, sulfur-containing insect growth regulators (Ujváry et al., 1992), we prepared a series of projuvenoids of the carbamate juvenoid fenoxycarb (Dorn et al., 1981). Here we describe the synthesis of typical *N*-sulfenylated, *N*-sulfinylated, as well as *N*-sulfonylated derivatives of fenoxycarb and related carbamates, and report on their comparative juvenile hormone-like activity observed in the laboratory with the large white butterfly, *Pieris brassicae* L. (Lepidoptera: Pieridae) and the rice weevil, *Sitophilus oryzae* L. (Coleoptera: Curculionidae). The results of a field experiment with the tobacco whitefly, *Bemisia tabaci* Gennadius (Homoptera: Aleyrodidae) are also summarized.

MATERIALS AND METHODS

General

^{1}H NMR spectra were recorded in deuterochloroform at either 80 or 250 MHz on Bruker AW-80 or WM-250 spectrometers (Rheinstetten, Germany), respectively. Chemical shifts are referenced to Me_4Si as the internal standard and expressed in ppm. IR spectra were measured in CCl_4 solution with a Bruker IFS-113v FT-IR spectrophotometer. Elemental analyses, performed by the Microanalytical Laboratory, Eötvös Lóránd University, Budapest, Hungary, correspond to calculated values for C, H, N, and S. Analytical TLC was performed on 0.25 mm silica gel plates (Merck, Darmstadt, Germany) developed with benzene/ethyl acetate (90:10). Preparative column chromatography was carried out using silica gel 60 (0.063–0.29 mm) (Reanal, Budapest) and either benzene/ethyl acetate/triethylamine (95:5:0.1) (eluent A) or hexane/ethyl acetate/triethylamine (90:10:0.1) (eluent B) for elution.

*Abbreviations used: JH = juvenile hormone.

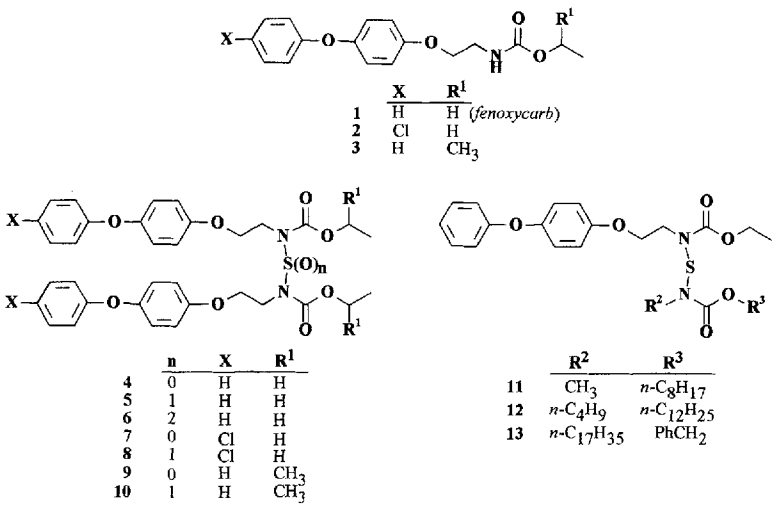

Fig. 1. Structures of carbamate juvenoids and their projuvenoid derivatives.

Chemicals

Analytical grade solvents were dried by conventional procedures. Thionyl chloride was freshly distilled. Sulfur dichloride (SCl_2) was distilled over PCl_5 (0.5% by weight of SCl_2) under nitrogen atmosphere and the fraction boiling between 53 and 70°C was collected. This fraction was redistilled in the same manner and the fraction boiling at 56–60°C was used.

Fenoxycarb (1) and the related starting materials 2 and 3 were prepared as described by Fischer et al. (1978). The new projuvenoids were synthesized using procedures developed earlier for proinsecticide carbamates. Specifically, symmetrical derivatives 4, 5, and 7–10 in which two identical moieties are connected with a -S- or -S(O)- bridge were obtained in 50–75% yields from the carbamate and SCl_2 or $SOCl_2$, respectively (Fahmy et al., 1974; Fahmy and Fukuto, 1983). *Bis*sulfonylcarbamate 6 was prepared by acylation of the appropriate *bis*sulfonamide (McDermott and Spillane, 1984). Unsymmetrical derivatives 11–13 were obtained in 45–70% yields according to known procedures (Fahmy et al., 1978; Brown and Kohn, 1974) by reacting fenoxycarb with the *N*-chlorosulfenyl derivative (Brown, 1972) of the corresponding carbamates. The following procedures are typical for the synthesis of representative projuvenoids (Fig. 1).

Ethyl *N,N'*-Sulfenyl-Bis[2-(4-Phenoxyphenoxy)Ethyl Carbamate] (4)

To an ice cooled solution of carbamate 1 (3.2 g, 10 mmol), *N,N*-(4-dimethylamino)pyridine (0.37 g, 3.0 mmol) and 0.9 ml pyridine in 20 ml CH_2Cl_2 was added SCl_2 (0.35 ml, 5.5 mmol) and the solution was stirred at ambient temperature for 18 h. Then the mixture was diluted with $CHCl_3$, washed with 5% aq. HCl solution, saturated $NaHCO_3$ solution and water, dried (Na_2SO_4) and concentrated in vacuum. The residue was purified by column chromatography (eluent A) to give 1.56 g (50%) of 4 as light viscous oil.

IR: ν 1,711 (C=O), 1,219, and 1,121 cm^{-1}. ^1H NMR: δ 1.32 (6H, t, J = 7.3 Hz, CH_3), 4.14 (8H, m, OCH_2CH_2N), 4.23 (4H, q, J = 7.3 Hz, OCH_2), 6.8–7.05 (14H, m, aromatic H), 7.25–7.30 (4H, m, aromatic H).

Ethyl *N,N´*-Sulfinyl-Bis[2-(4-Phenoxyphenoxy)Ethyl Carbamate] (5)

To an ice cooled solution of carbamate 1 (4.0 g, 13.2 mmol) and triethylamine (2.2 ml, 16 mmol) in 12 ml THF was added $SOCl_2$ (0.50 ml, 6.8 mmol) and the solution was stirred at ambient temperature for 18 h. Then the reaction mixture was diluted with 20 ml of diethyl ether and 20 ml of hexane and worked up as described above. The crude product was purified by column chromatography (eluent A) to give 3.00 g (71%) of biscarbamate 5 as a light yellow oil.

IR: ν 1,717 (C = O), 1298 (S = O), 1,221, and 1,130 cm^{-1}. ^1H NMR: δ 1.35 (6H, t, J = 7.1 Hz, CH_3), 3.94 (4H, t, J = 6.0 Hz, NCH_2), 4.14 (4H, t, J = 6.0 Hz, OCH_2), 4.31 (4H, q, J = 7.1 Hz, OCH_2), 6.8–7.05 (14H, m, aromatic H), 7.25–7.30 (4H, m, aromatic H).

Ethyl *N,N´*-Sulfonyl-Bis[2-(4-Phenoxyphenoxy)Ethyl Carbamate] (6)

A mixture of (4-phenoxyphenoxy)ethylamine (3.0 g, 13.0 mmol) and sulfamide (0.47 g, 4.9 mmol) was stirred at 140°C for 8 h. The reaction mixture was cooled to room temperature, 5 ml of ethanol and 5 ml of 15% aq. HCl solution were added, the precipitate was collected and recrystallized from ethanol containing 2% dimethyl sulfoxide to yield 1.5 g (44%) of *N,N´*-di[2-(4-phenoxyphenoxy)ethyl]sulfamide as white crystals, mp 144–146°C. A suspension of this compound (0.52 g, 1.0 mmol), ethyl chloroformate (0.44 ml, 4.6 mmol), pulverized anhydrous K_2CO_3 (1.48 g, 10 mmol), and 20 ml anhydrous acetone was stirred at reflux temperature for 10 h. The reaction mixture was then filtered, the filtrate concentrated and the residue recrystallized from ethanol to give 0.60 g (90%) of product 6 as white crystals, mp 105–106°C.

IR: ν 1,737 (C = O), 1,392 (O = S = O), 1,310, 1,171, 1,150, 1,130, 561 cm^{-1}. ^1H NMR: δ 1.34 (6H, t, J = 7.1 Hz, CH_3), 4.12 (8H, m, OCH_2CH_2N), 4.22 (4H, q, J = 7.1 Hz, OCH_2), 6.9–7.1 (14H, m, aromatic H), 7.3 (4H, m, aromatic H).

Ethyl *N,N´*-Sulfenyl-Bis[2-(4-Chlorophenoxyphenoxy)Ethyl Carbamate] (7)

This oily compound was prepared from the appropriate carbamate derivative by the method described for compound 4.

IR: ν 1,715 (C = O), 1,219, and 1,121 cm^{-1}. ^1H NMR: δ 1.28 (6H, t, J = 7.0 Hz, CH_3), 4.14 (8H, m, OCH_2CH_2N), 4.23 (4H, q, J = 7.0 Hz, OCH_2), 6.85–6.97 (12H, m, aromatic H), 7.23–7.26 (4H, m, aromatic H).

Ethyl *N,N´*-Sulfinyl-Bis[2-(4-Chlorophenoxyphenoxy)Ethyl Carbamate] (8)

This oily compound was obtained from the appropriate carbamate derivative as described for compound 5.

IR: ν 1,717 (C = O), 1,298 (S = O), 1,221, and 1,130 cm^{-1}. ^1H NMR: δ 1.28 (6H, t, J = 7.1 Hz, CH_3), 3.94 (4H, t, J = 6.0 Hz, NCH_2), 4.14 (4H, t, J = 6.0 Hz, OCH_2), 4.31 (4H, q, J = 7.1 Hz, OCH_2), 6.85–6.97 (12H, m, aromatic H), 7.23–7.26 (4H, m, aromatic H).

Isopropyl *N,N'*-Sulfenyl-Bis[2-(4-Phenoxyphenoxy)Ethyl Carbamate] (9)

This oily compound was obtained from the appropriate carbamate derivative as described for compound 4.

IR: ν 1,707 (C = O), 1,221 and 1,120 cm^{-1}. ^1H NMR: δ 1.30 (12H, d, J = 6.0 Hz, CH_3), 4.14 (8H, m, $OCH^{-1}CH^{-1}N$), 4.98 (2H, sept, J = 6.0 Hz, OCH), 6.9–7.1 (14H, m, aromatic H), 7.3 (4H, m, aromatic H).

Isopropyl *N,N'*-Sulfinyl-Bis[2-(4-Phenoxyphenoxy)Ethyl Carbamate] (10)

This oily compound was obtained from the appropriate carbamate derivative as described for compound 5.

IR: ν 1,717 (C = O), 1,375, 1,296, 1,221, 1,130, and 1,105 cm^{-1}. ^1H NMR: δ 1.27 (12H, d, J = 6.0 Hz, CH_3), 3.88 (4H, t, J = 6.0 Hz, NCH_2), 4.10 (4H, t, J = 6.0 Hz, OCH_2), 5.05 (2H, sept, J = 6.0 Hz, OCH), 6.9–7.1 (14H, m, aromatic H), 7.3 (4H, m, aromatic H).

Ethyl *N*-[(*n*-Octyloxycarbonyl-Methylamino)Sulfenyl]-2-(4-Phenoxyphenoxy)Ethyl Carbamate (11)

To an ice cooled solution of carbamate 1 (2.0 g, 6.6 mmol) in pyridine was added *n*-octyl *N*-(chlorosulfenyl)methylcarbamate (1.5 g, 8.0 mmol) and the solution was stirred at ambient temperature for 16 h. The reaction mixture was then diluted with 20 ml of diethyl ether and 20 ml of hexane, the precipitate filtered, and the filtrate worked up as described above. The crude product was purified by column chromatography (eluent B) to give 3.1 g (90%) of biscarbamate 11 as a light brown viscous oil.

IR: ν 1,709 (C = O), 1,279, 1,225, and 1,121 cm^{-1}. ^1H NMR: δ 0.87 (3H, t, J = 7.0 Hz, CH_3), 1.0–1.65 (15H, m, aliphatic CH_2 and CH_3), 3.38 (3H, s, NCH_3), 4.1–4.25 (8H, m, NCH_2 and OCH_2), 6.8–7.0 (7H, m, aromatic H), 7.22 (2H, m, aromatic H).

Ethyl *N*-[(*n*-Dodecyloxycarbonyl-Butylamino)Sulfenyl]-2-(4-Phenoxyphenoxy)Ethyl Carbamate (12)

This oily compound was prepared from the appropriate carbamate derivatives as described for 11. IR: ν 1,713 (C = O), 1,275, 1,221, and 1,119 cm^{-1}. ^1H NMR: δ 0.9 (6H, m, CH_3), 1.0–1.6 (27H, m, aliphatic CH_2 and CH_3), 4.0–4.3 (10H, m, NCH_2 and OCH_2), 6.8–7.0 (7H, m, aromatic H), 7.23 (2H, m, aromatic H).

Ethyl *N*-[(*n*-Benzoyloxycarbonyl-Heptadecylamino)Sulfenyl]-2-(4-Phenoxyphenoxy)Ethyl Carbamate (13)

This compound was prepared from the appropriate carbamate derivatives as described for 11 and the crystalline product was recrystallized from hexane to give 13 as a pale yellow powder, mp 57–59°C.

IR: ν 1,709 (C = O), 1,225, and 1,121 cm^{-1}. ^1H NMR: δ 0.88 (3H, t, J = 7.0 Hz, CH_3), 1.2–1.7 (33H, m, aliphatic CH_2 and CH_3), 3.72 (2H, t, J = 7.5 Hz, NCH_2), 4.0 (4H, m, OCH_2CH_2N), 4.2 (2H, q, J = 7.0 Hz, OCH_2), 5.17 (2H, s, OCH_2), 6.8–7.5 (14H, m, aromatic H).

Laboratory Bioassays

P. brassicae. Twenty-four-hour-old last instar (L_5) larvae were selected from laboratory colonies reared on cabbage plants at 25 ± 2°C (18:6 L:D, 50 ± 5% relative humidity). The test compounds were dissolved in acetone and 2 µl of this solution was applied topically to the dorsal surface of the larvae (25 to 50 larvae per dose). Groups of 10 to 15 treated larvae were kept in plastic cups and fed continuously with fresh cabbage leaves. The morphogenetic activity of the test compounds was determined after pupal ecdysis based on a scoring system (from 0 = normal pupa to 4 = larval-pupal intermediate resembling to a supernumerary larval instar) (Varjas, 1985). The activities are expressed as ID_{50} values, a dose of the test compound causing intermediate larval forms with large cuticular areas on the head and thorax; completely everted wings; larval type abdomen (score 2), calculated by linear regression analysis from the average score of each treatment.

S. oryzae. The experiments were carried out as described previously (Kramer et al., 1981). Briefly, 100 g batches of wheat kernels that had been cleaned and tempered to approximately 10% moisture were treated with 5 ml of acetone solution to obtain 1 to 100 ppm of the test compounds on the diet after mixing thoroughly. The treated kernels were allowed to equilibrate for 24 h before testing. Then 100 g wheat in pint jar was infested with 50 adult beetles obtained from cultures maintained at the U.S. Grain Marketing Research Laboratory. All experiments were conducted at 27 ± 2°C and 60 ± 5% relative humidity. Four replicates were used for each dose. After 21 days of exposure the original parent insects were removed and the activity of the chemicals was determined by counting the total dead and live progeny after 9 weeks. Values were corrected for mortality in untreated samples.

Field Test

B. tabaci. A single trial in cotton was carried out in Faisalabad, Pakistan, using four replicates late in the summer of 1990. Experimental plots were sprayed once with the given dose of either an emulsifiable concentrate of projuvenoid 5 (25 EC with acetone as solvent and Citowett, BASF AG, Limburgerhof, Germany, as wetting agent), wettable powder of 1 (Insegar 25 WP; La Quinoleine, Paris, France) or an insecticide standard Polytrin-C EC-400 (a formulation containing profenofos and cypermethrin, 400 and 40 g/l, respectively). For evaluation, the white fly population was assessed by determining the percentage of normal nymphs and adults separately on ten randomly selected plants in every plot on the 12th day after spraying.

RESULTS

The results of the laboratory assays with projuvenoids topically applied to last instar *P. brassicae* larvae are summarized in Table 1. The symmetrical sulfenyl and sulfinyl derivatives (4 and 5, respectively) and the unsymmetrical sulfenyl projuvenoids 11 and 12, being the most potent compounds, were about six- to eight-fold more active than the parent fenoxycarb (1). The inactive sulfonyl compound (6) is apparently too stable to release the active juvenoid.

TABLE 1. Morphogenetic Activity of Topically Applied Juvenoids on Fifth Instar Larvae of the Large White Bufferfly, *Pieris brassicae

Compound	ID_{50} (ng/larva)	Confidence limits at $P = 95\%$
Parent carbamates		
1 (fenoxycarb)	21	18–24
2	22	19–25
3	24	18–29
Projuvenoid derivatives		
4	2.8	0.5–5.1
5	2.2	1.1–3.3
6	>100	
7	26	23–29
8	9	3–15
9	22	21–23
10	20	19–21
11	3.4	3.0–3.8
12	2.8	1.5–4.1
13	6.4	5.7–7.1

*For comparison, the corresponding ID_{50} value for methoprene is 60 ng/larvae in this assay.

The results of the comparative bioassay using the stored product pest *S. oryzae*, an internal grain feeder, are shown in Figure 2. When the test compounds were mixed with grain at the 1 ppm dose to suppress progeny development, all derivatives provided uniformly better protection against this insect than did two commercially available grain protectants, malathion and methoprene, but none of them surpassed fenoxycarb (1) in activity. Under these conditions the new juvenoids enter the body of this insect mainly by feeding and not by contact such as occurs with topical application. Therefore, differences in lipophilicity affecting penetration through the cuticle are of less significance for this type of treatment. Relative to fenoxycarb, the

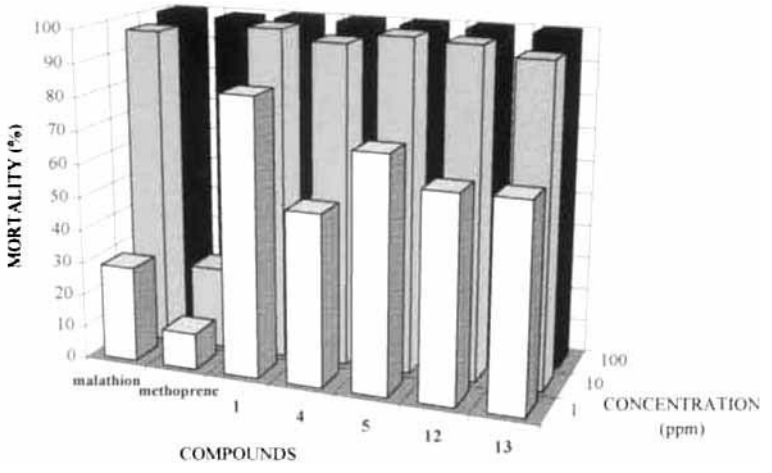

Fig. 2. Suppression of progeny development in wheat of the rice weevil, *Sitophilus oryzae*, by malathion and (pro)juvenoids.

projuvenoid compounds might not be taken up in sufficient quantity by the weevil, because the lipophilic derivatives might not penetrate the kernel efficiently.

In a small-scale field experiment in cotton with *B. tabaci*, a homopteran shown to be sensitive to fenoxycarb (Satoh and Plapp, 1993), the symmetrical biscarbamate 5, showing generally good activity in the other tests, at 100 g/ha was comparable to fenoxycarb (1) at 200 g/ha in suppressing nymph and adult emergence. Compound 5 was also more active than the commercial neurotoxic insecticide mixture applied at 500 g/ha (Table 2). The chemical modification of fenoxycarb to a projuvenoid structure improved the field performance against this test species although the possibility that activity differences might partly be caused by the different formulations (liquid vs. wettable powder) cannot be discounted.

DISCUSSION

A large number of proinsecticides, several of commercial importance, have been prepared and studied in detail, but no reports on structurally related projuvenoids have appeared in the scientific literature. Therefore, we decided to study how similar modifications of fenoxycarb-type carbamates affect their JH-like activity anticipating that suitable derivatization of the carbamate moiety would yield (pro)juvenoid compounds with improved biological properties and different activity spectrum.

This expectation was fulfilled as the results of laboratory and field experiments using these projuvenoids with representative insect species demonstrate. The greatly enhanced activities of some of the projuvenoids can be attributed to their increased lipophilicity relative to fenoxycarb. Lipophilicity, as measured by the *n*-octanol/water partition coefficient and usually expressed as the compound's log P value, is an important factor in governing activity as quantitative structure-activity studies for terpenoid juvenoids related to methoprene established (Nakayama et al., 1984). Fenoxycarb has a

TABLE 2. Effect of Juvenoids and an Insecticide on Tobacco Whitefly, *Bemisia tabaci*, Population in a Cotton Field (Faisalabad, Pakistan, August 1990)

Treatment and formulation	Dose of active ingredient (g/ha)	Percentage of normally developed insects 12 days after treatment	
		Nymph	Adult
Compound 5, 25 EC	50	47	36
	100	33	31
	200	16	19
Fenoxycarb (1), 25 WP	100	41	43
	200	34	29
	400	21	20
Polytrin-C, 400 EC	500[a]	78	89
Untreated control	—	92	89

[a]A mixture of profenofos (455 g/ha) and cypermethrin (45 g/ha).

log P of 4.07, whereas for methoprene this value is 5.21 (Tomlin, 1994), indicating that the carbamate analog is less lipophilic than the sesquiterpenoid ester. For structurally diverse groups of neurotoxic carbamate insecticides the replacement of the acidic proton of the carbamate moiety with a nonpolar sulfenylcarbamate or sulfinylcarbamate group renders the molecule more lipophilic and substituent-dependent increases in lipophilicity by log P increments of 1.5 to 4.0 are observed (Fahmy et al., 1978; Fukuto, 1983). Consequently, analog derivatizations of fenoxycarb should afford compounds with log P values significantly higher than that of the parent carbamate.

The mode of action of the projuvenoids is the same as that of the conventional juvenoids except that the active principle is released by abiotic or biotic factors in the insect after treatment. This activation process appears to be mainly non-enzymatic since studies with sulfenylated derivatives of carbofuran and related neurotoxic insecticides show that -SH group containing compounds readily cleave them to their parent carbamates (Chiu et al., 1975; Collins et al., 1980; Wallace and Zerba, 1989). In model experiments monitored by ^{1}H NMR spectroscopy, we observed that two equivalents of 4-nitrothiophenol liberate fenoxycarb from the *N*-sulfenyl and *N*-sulfinyl carbamates 4 and 5 (the respective half-lives are about 25 days and 25 h in $CDCl_3$ solution). The *N*-sulfonyl derivative 6, in agreement with the results obtained for *N*-arylsulfonyl proinsecticides (Kinoshita and Fukuto, 1980), withstands these conditions for weeks even in the presence of trifluoroacetic acid, which explains the lack of JH activity for this compound.

The derivatizing carbamate moieties of the unsymmetrical projuvenoids, also liberated in the activation process, are essentially devoid of hormonal activity as was shown for *P. brassicae* (their ID_{50} value is >15,000 ng/larva) and for the termite *Reticulitermes flavipes* (Okot-Kotber et al., 1991) using doses of the aliphatic carbamate at least two orders of magnitude higher than that of fenoxycarb. These data again corroborate that the increased hormonal effect should be attributed to the altered physicochemical properties of the projuvenoids relative to the parent compound.

In summary, results of laboratory and field experiments demonstrate that an appropriate derivatization technique applied to carbamate type juvenoids could result in a substantial increase in JH activity and, if necessary, the chemistry can be "tailored" to suit particular biological requirements. The optimal lipophilicity attained by suitable derivatization facilitates movement through tissues or membranes to the site of action as well as protects the parent compound from premature metabolism. In addition, the structural modification used can also introduce a "delay factor" that provides a slow-release chemical formulation within the insect body, thus sustaining a sufficient juvenoid level for an extended period. However, good efficacy of the projuvenoids obtained in laboratory experiments does not directly translate into improved performance in the field because other factors such as differential uptake and lability of the derivatives to various environmental conditions can diminish the effect of the chemical modification.

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